[redacted]

JS 9/15/21
RJA 1/18/22

Case No. P-18-0152

Chemical Name: [redacted]
CASRN: [redacted]

ASSIGNMENTS	NAME	DATE
SAT Chair	W Irwin	SAT Date 5/1/18
HH Hazard Assessor (A)	K Jacobs	SAT Date 5/1/18
HH Hazard QC Reviewer (A)	Cal Baier-Anderson	5/3/18
HH Risk Assessor FOCUS (B)	Sailesh Surapureddi	05-10-2018
HH Risk QC Reviewer (B)	Sharon Oxendine	05/09/18

Human Health Report Status:	DATE COMPLETED
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

Updated 10/31/18 to clarify risk language and add PUI

[redacted]

1 HUMAN HEALTH SUMMARY

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties, available PMN data, and by comparing it to structurally analogous chemical substances for which there is information on human health hazard.
Based on the hazard determination and available qualitative risk information, EPA concludes that there is not risk for the PMN substance. The risk estimates for this chemical are for the intended conditions of use.

1.1 Hazard Summary

- The absorption is expected to be poor dermally, good by the lungs and poor in the GI tract based on p-chem properties.
- There is concern for corrosion to all tissues due to the [redacted] (SDS) and analogs
- There is concern for eye irritation and sensitization based on analog data.
- There is concern for lung toxicity based on analogs and irritation/corrosion hazards.

1.2 Risk Summary

1.2.1 Workers

- Although analog data and information provided in the new chemical category document indicates that the PMN could result in adverse lung effects, risks were not identified for workers via inhalation because exposure is negligible.

- Risks for eye irritation, skin corrosion and sensitization cannot be quantified due to lack of dose-response for these hazards. Exposures would be mitigated with use of appropriate PPE, including gloves and eye protection. EPA expects the PPE indicated in the Safety Data Sheet for the PMN substance, will be used by workers. Therefore, EPA does not expect risk for eye irritation, skin corrosion and sensitization.

1.2.2 General Population

- Risks were not identified for the general population for irritation, corrosion and sensitization via consumption of drinking water or fish ingestion because these hazards are not a concern for these routes of exposure due to the effect of dilution.
- Risks were not identified for lung toxicity via inhalation exposure since exposures were below modeling thresholds.

[redacted]

1.2.3 Consumers

Risks to consumers were not evaluated because consumer uses were not identified as conditions of use.

1.3 Potentially Useful Information:

Potentially useful information would inform understanding of:
Dermal toxicity
Skin Sensitization

[redacted]

2 HUMAN HEALTH HAZARD- PART A

2.1 Chemistry Summary

PMN: P-18-0152

Submitter: [redacted]

CRSS Date: Apr 30, 2018

Max. PV (Kg): [redacted]

Binding Option Marked: false

Manu.: X

Import:

MW:

% <500:

% <1000:

CASNO: [redacted]

Structure: [redacted]

	Meas.	Est.
MP		
BP		327
Pres.		
VP		
S-H2O		1000
Log P		

Chemical Name: [redacted]

Analogs: [redacted]

Smiles of pictured structure: [redacted]

Use: [redacted]

2.1 SAT Summary

2.1.1 PMN Health Rating

H = 2

2.1.2 SAT Key Words

IRR-E, SENS; CORR; AquaTox

2.1.3 Absorption

The absorption is expected to be poor dermally, good by the lungs and poor in the GI tract based on p-chem properties.

2.1.4 SAT Health Summary

There is concern for corrosion due to the [redacted] (SDS), eye irritation and sensitization based on an analog.

[redacted]

2.1.5 PMN Data (Study summary, POD)

[redacted]

All submitted data was for the analogs above – [redacted], which are much more toxic than the PMN.

QSAR alerts – DEREK, Oasis
- Plausible skin sensitization (for metabolites)
- Negative for genotoxicity

in vivo dermal irritation – [redacted] in rabbits
- Negative for any signs of irritation [redacted]
- Study summary for [redacted] showed slight redness and swelling indicating slight irritation.

in vivo dermal irritation – [redacted] in rabbits
- Positive for dermal irritation based on well-defined erythema (redness), desquamation (peeling), and slight edema. Irritation was reversible in all rabbits. There were no systemic effects.
- Study summary showing negative results for skin corrosion in rabbits.

in vivo eye irritation – [redacted] in rabbits
- Positive for severe eye irritation with pain response, conjunctival redness, swelling, discharge, and corneal opacity. Effects were not reversible for all 4/6 rabbits. One rabbit died 12 days after administration, however necropsy could not determine a cause of death, and the rabbit had previously not been eating.

in vivo eye irritation – [redacted] in rabbits
- Positive for severe eye irritation with irritation, red coloration, swelling, discharge, corneal opacity, and vascularization. Effects were not reversible in 2/3 rabbits. There were no systemic effects.

Acute oral toxicity - [redacted] in rats
- Calculated LD_{50} = 196 mg/kg. Signs of toxicity exhibited by rats include cyanosis, ataxia, prostration, glossy eyed appearance, and lethargy. The toxic effects of [redacted] indicate

[redacted]

that the central nervous system is most likely the target organ. Autopsy of animals that died during the study revealed severe inflammation of the gastrointestinal tract. No gross pathological alterations in the organs or tissues were noted in any of the surviving animals at terminal necropsy. Death generally occurred within two hours after dosing. No instances of delayed mortality were observed.

- Study summary for Z-8038 gave LD_{50} = 653 mg/kg. Signs of toxicity exhibited by rats included extreme lethargy, ataxia, convulsions, and coma. Necropsy of the rats that died during the study showed hemorrhagic conditions of the gastrointestinal tract.

Acute oral toxicity - [redacted] in rats

- Calculated LD_{50} = 1897 in females, 2574mg/kg in males (deaths at 3000 and 5000 mg/kg). Clinical signs of reaction to treatment comprised piloerection (among rats at all dosages), hunched posture, waddling/unsteady gait, pallid extremities, eyes dulled, increased salivation, abnormal respiration, ungroomed appearance, faecal disturbances, increased sensitivity and increased lacrimation (among rats at 1200, 3000 and/or 5000 mg/kg), walking on toes, blue/cold extremities, lethargy, partially closed eyelids and body tremors (among rats at 3000 and 5000 mg/kg) and prostration (5000 mg/kg only). Effects were reversible in surviving rats.

Acute dermal toxicity – [redacted] in rabbits

- LD_{50} > 2000mg/kg. There were no deaths; with the exception of few feces in one female rabbit on day 3, there was no evidence of any systemic response to treatment in any animal during the study. Persistent slight to moderate irritation (erythema with or without edema up to Grade 3) was evident in all rabbits. These reactions had notably ameliorated by the second week of the study with resolution in all but three animals complete by Day 15. In the three remaining rabbits slight erythema (Grade 1) was still evident at study termination. Also notable in all rabbits during the first days following treatment was a very dry texture to the skin over the treatment site, desquamation of the skin on the treatment site (notable in all rabbits and present in six rabbits at study termination) and in one rabbit localised necrosis/blanching evident throughout the observation period. There was slight to notable weight loss in three females but this was considered of no toxicological significance.

Acute dermal toxicity - [redacted] (study summary)

- LD_{50} > 2000mg/kg. No effects on body/organ weight, pathological changes, or clinical signs.

Acute inhalation toxicity - [redacted] in rats (whole-body exposure)

- LC_{50} between 1.49 and 2.44 mg/L (deaths at 2.44 and 5.75 mg/L). Rats exhibited exaggerated breathing and partially closed eyes during exposure (perhaps due to airflow being too high?). During the observation period, rats exhibited irregular, noisy and/or exaggerated breathing, partially closed eyes, lethargy, and ataxia. Clinical signs are indicative of neurological toxicity. There were also dose-dependent decreases in body weight and secondary decreases in liver weight. Severely congested lungs were observed in all deceased rats; congestion and pale hardened areas were observed in some exposed surviving rats. Lung weights were increased in surviving female rats at high doses.

Acute inhalation toxicity - [redacted] (study summary)

- LC_{50} > 0.6 mg/L. No effects on body/organ weight, pathological changes, or clinical signs.

[redacted]

Ames reverse mutation assay - [redacted]
- Negative for mutagenicity both with and without S9 activation

Ames reverse mutation assay – [redacted]
- Negative for mutagenicity both with and without S9 activation

Skin sensitization (Guinea Pig Maximization Test) - [redacted] (study summary)
- Moderately sensitizing. 45% of animals exhibited a sensitization response.

28-day inhalation study – [redacted] (6h/day, 5d/week, nose-only exposure)
- One high-dose male was found dead on study day 1 and the surviving males and females in the high-dose group were euthanized in extremis on study day 1due to severe clinical observations and respiratory distress. Prior to death, the high-dose males and females were noted with clinical observations of unkempt appearance, pale extremities, partial closure of the eye(s), cool extremities and body, labored respiration, gasping, red material around the eye(s), mouth, and/or nose and on the forelimb(s), yellow material on the urogenital area, ventral trunk, and anogenital area, and/or white material on the dorsal head. High-dose animals also exhibited body-weight loss. Gross observations of dark red discoloration of all lung lobes correlated microscopically with marked congestion. In addition, necrosis of the respiratory epithelium was observed in the sections of trachea present in the lung sections of the animal found dead. Effects at lower doses included thin body condition, reduced body weight, reduced food consumption, fully collapsed lungs, increased lung weights, acute inflammation and degeneration/ regeneration of the respiratory and olfactory epithelium, microscopic findings in the larynx and trachea, and increased alveolar macrophages and luminal debris in lungs. NOAEC = 10mg/m^3
Note: This was not reviewed due to being deemed not an appropriate analog

Reproductive/fertility toxicity (OECD 414 7-day range finding) – [redacted]
- Doses of 750 and 1000 mg/kg. One rat died at 750 mg/kg. Slight body weight losses that were not significant in the high dose, and minor clinical signs observed including rales (rattling sound in lungs) and clear material around mouth. No pathological findings. Doses of 100, 750 and 1000mg/kg chosen for full study.
Note: This was not reviewed due to being deemed not an appropriate analog

Reproductive/developmental toxicity (OECD 422) – [redacted]
- Doses of 0, 25, 125, and 500 mg/kg. A few deaths at 500mg/kg. Clinical findings attributed to test substance included clear perioral soiling in several high-dose animals and either increased nasal sounds, labored respiration, or soft vocalizations in approximately half of the high-dose females and one high-dose male. There was dose-dependent resistance to dosing and salivating/wetness around mouth prior to dosing. No effects on body weight, FOB, hematology/serum chemistry, organ weights, or histopathological findings. Litters not produced in 2 high and 1 low-dose female, but no consistent reproductive or developmental effects were observed. NOAEL = 500mg/kg for mortality.
Note: This was not reviewed due to being deemed not an appropriate analog

[redacted]

2.1.6 Analog Data (analog, structure, study summary, POD)

[redacted]

Expect absorption and/or reaction all routes. According to the MSDS this compound is corrosive. Both the reactive silyl bonds and the amines will contribute to the compound's potential to be irritating and/or corrosive. Moderate concern.

8e data - resembles [redacted]

[redacted]

Dermal sensitizer in guinea pigs

[redacted]

- 2-WEEK INHALATION STUDY (0.1, 1, 10 MG/M3) - 1/10 DIED AT 10 MG/M3, LUNG TOXICITY IN ANIMALS AT 10 MG/M3
- ACUTE INHALATION STUDY IN MALE RATS - 4 HR ALC=250 MG/M3
- 2-DAY INHALATION STUDY (6HR/DAY)AT 35 MG/M3 - 1/6 DIED AT END OF 2ND EXPOSURE, MODERATE TO SEVERE WEIGHT LOSS
- 6-DAY STUDY (6HR/DAY) AT 1 & 10 MG/M3, SLIGHT BODY WEIGHT LOSS

2.1.7 Other Information (SDS, structural alert or component of interest, basis, etc.)

SDS – for mixture including methanol
May cause damage to organs (eyes, central nervous system)
Toxicity summaries are specific to methanol. SDS therefore not relevant to PMN

Submitter also included a risk assessment based on read-across DNEL and estimated exposure levels.

[redacted]

[redacted]

2.1.8 Exposure Routes of Interest

Route of Interest	
X	Inhalation:
X	Dermal:
X	Ingestion:

2.2 Human Health Category (From US EPA 2010 document)

Chemical Category: Choose an item. N/A
Chemical Category Health Concerns: --
Category Testing Strategy: --

2.3 Point of Departure Selected and Basis

2.3.1 POD for inhalation exposures

POD type: NOAEC
POD Value: 10 mg/m^3
POD Chemical:– [redacted]
POD Route: inhalation
POD Hazard Endpoint: thin body condition, reduced body weight, reduced food consumption, fully collapsed lungs, increased lung weights, acute inflammation and degeneration/ regeneration of the respiratory and olfactory epithelium, microscopic findings in the larynx and trachea, and increased alveolar macrophages and luminal debris in lungs
POD Basis: worst-case POD
POD Benchmark MOE: 100
Reference: 28-day inhalation study – [redacted]
Note: This POD is based on an analogue that was deemed not appropriately pertinent to this PMN due to containing additional structural alerts for trimethoxysilanes. However, it could be used as a worst-case analog purely to rule out risk.

[redacted]

3 HUMAN HEALTH RISK (PART B)

3.1 USES and EXPOSURES

3.1.1 Uses

[redacted]

3.1.2 Worker Exposure

3.1.2.1 Inhalation

negligible (VP < 0.001 torr).

3.1.2.2 Dermal

Potential Dose Rate: [redacted] mg/day over [redacted] days/yr

3.1.3 General Population Exposure:

3.1.3.1 Drinking Water

ADR as high as 5.12E-06 mg/kg/day

3.1.3.2 Fish

ADR as high as 1.99E-07 mg/kg/day

3.1.3.3 Air/Inhalation

below modeling thresholds

Exposure Scenario[1]	Water						Landfill	Stack Air		Fugitive Air	
Release activity(ies)[2]; exposure calculation(s)[3]	Drinking Water		Fish Ingestion		7Q10[4] CC = 3	PDM Days Exceeded	LADD	ADR (24-hr conc.)	LADD (Annual conc.)	ADR (24-hr conc.)	LADD (Annual conc.)
	ADR	LADD	ADR	LADD							
	mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day	µg/l	# Days	mg/kg/day	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)	mg/kg/day (µg/m^3)
USE:Max ADR: max acute eco	**5.12e-6**	--	**1.99e-7**	--	**1.80e-1**	--	--	-- (--)	-- (--)	-- (--)	-- (--)
USE:PDM	--	--	--	--	**1.80e-1**	--	--	-- (--)	-- (--)	-- (--)	-- (--)
USE:Max LADD	--	**2.58e-8**	--	**1.86e-10**	--	--	**1.09e-5**	-- (--)	-- (--)	-- (--)	-- (--)

3.1.4 Consumer Exposure

None

3.2 RISK CALCULATIONS

3.2.1 Worker Calculations

- Although analog data and information provided in the new chemical category document indicates that the PMN could result in adverse lung effects, risks were not identified for workers via inhalation because exposure is negligible.

[redacted]

- Risks for eye irritation, skin corrosion and sensitization cannot be quantified due to lack of dose-response for these hazards. Exposures would be mitigated with use of appropriate PPE, including gloves and eye protection. EPA expects the PPE indicated in the Safety Data Sheet for the PMN substance, will be used by workers. Therefore, EPA does not expect risk for eye irritation, skin corrosion and sensitization.

3.2.2 General Population Calculations

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3.2.3 Consumer Calculations

Risks to consumers were not evaluated because consumer uses were not identified as conditions of use.